REMARKS

Rejection of the claims under 35 USC §112:

Claims 14-26 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The action states that the claims encompass a genus of unspecified chelators and polymers capable of associating with a polynucleotide. The Action suggests, on pages 4 and 8, that the specification only provides sufficient description of a chelator-polycationic polymer. Accordingly, Applicants have amended claim 14 to cite that primary amine-containing molecule is polycationic and that the chelator is capable of forming a non-covalent coordinate bond with a primary amine. Support for the amendment can be found in the specification on page 17 line 25 to page 18 line 18, and in example 15. Chelators, including crown ethers, known to form non-covalent coordinate bonds with primary amines are readily available in the art as evidenced by March "Advanced Organic Chemistry" Wiley and Sons (attached).

Claims 14-26 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Applicants believe the amendments to claim 14, described above in response to the written description requirement, are sufficient to overcome the rejection based on the enablement requirement.

Rejection of the claims under 35 USC §102:

Claims 14-26 have been rejected under 35 U.S.C. 102(b) as being anticipated by Kayyem et al. WO 96/11712. Applicants respectfully disagree. Kayyem teaches that a polychelator-polycation can be used to condense DNA. Metal ions, which are able to be coordinately bound by the chelators, can then be added to the DNA/polycation complex in order to co-deliver the DNA and the metal ions. In contrast, Applicants claim forming a complex of DNA and amine-containing polycation and then associating a chelator with amines on the polycation. The attached drawings illustrate the difference between the teaching of Kayyem and the invention claimed by the Applicants. Applicants respectfully request reconsideration of the 102 rejection.

Rejection of the claims under 35 USC §103:

Claims 14-26 have been rejected under 35 U.S.C. 103 as being unpatentable over Kayyem et al. in view of Hnatowich et al. U.S. Patnet No. 5,980,861. Applicants respectfully disagree for the reasons stated above in response to the 102 rejection. Applicants respectfully request reconsideration of the 103 rejection.

Double Patenting:

Claims 14-26 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,818,626.

Applicants respectfully disagree. Claims 1-11 of '626 encompass a polymer in which association of the polymer with a nucleic acid is dependent on the presence of metal cations (see attached illustration). In the instant application, association of the chelator with the nucleic acid is not dependent on the presence of metal cations. Claims 12-17 of '626 encompass metal cation dependent association of a second polymer with a first polymer (see attached illustration). The instant invention claims association of a chelator with a polycation through coordinate bonding of an amine on the polycation. Applicants request reconsideration of the double patenting rejection.

The Examiner's objections and rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that claims 14-16 and 18-26 should be allowable.

Respectfully submitted,

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608-238-4400

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as express mall in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

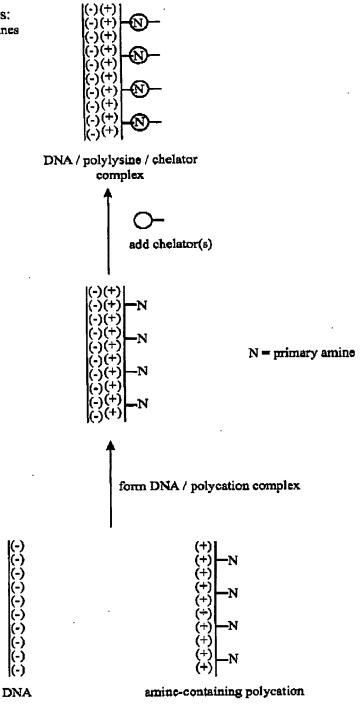
Kirk Ekena

[REPLACEMENT SHEET]

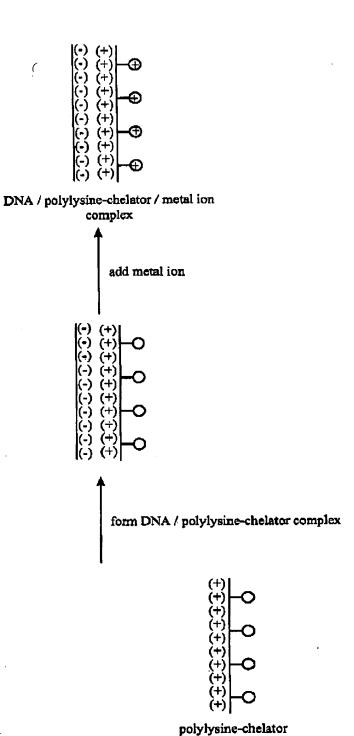
CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of Application No. 09/234,606, filed January 21, 1999, now U.S. Patent 6.818.626, which claims the benefit of U.S. Provisional Application No. 60/093,230, filed July 17, 1998.

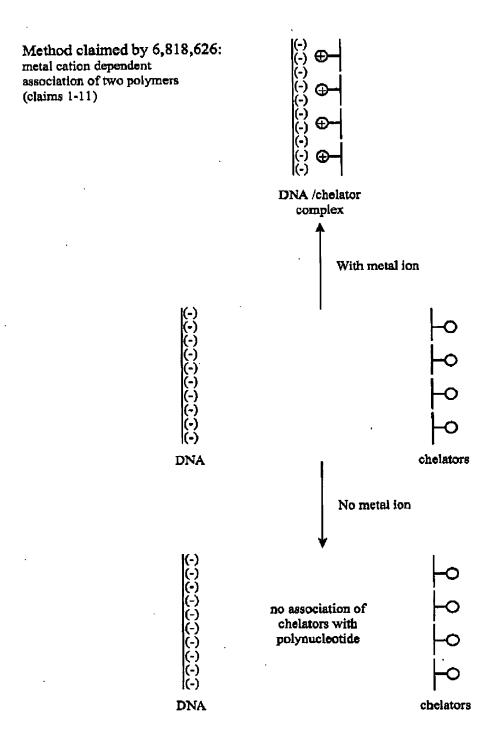
Method taught by Applicants: association of chelators with amines on polycations present in polycation/DNA complexes



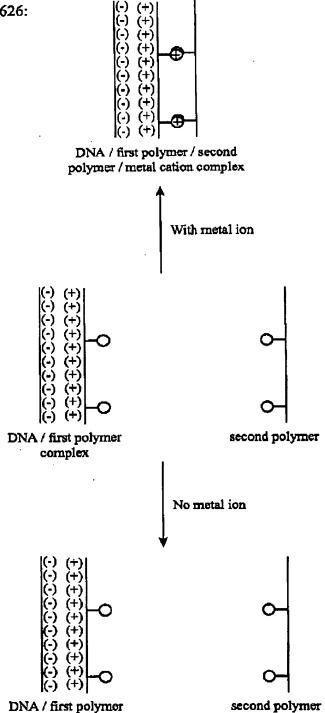
Method taught by Kayyem: association of polychelator with DNA followed by association of metal ion with polychelator



DNA



Method claimed by 6,818,626: metal ion dependent association of two polymers (claims 12-17)



complex

ADVANCED ORGANIC CHEMISTRY

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FOURTH EDITION

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> ভার পুরুষ কর্ম কর্ম বিশ্ব প্রকৃতি ক্রান্ত ক্রান্ত্রী কর্ম ক্রান্ত্রী ক্রান্ত্রী ক্রান্ত ক্রান্ত্রী ক্রান্ত্রী ক্রান্ত্রী

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BONDING WEAKER THAN COVALENT

drides. ³³ A particularly strong olefin acceptor is retracymoethylene. ³⁶ mbetitioents also act as acceptor suclecules as do curbon tetrahalides⁵⁴ and certain subty between phenois and quinoues (quinhydrones). St Olekus that contain electron-withdrawing Unfortunately, salts of pieric acid are also called picrates. Similar completes are formed

e.g. , nitromethane , with about the same dipole moment as nitrobenzene, forms much weaker exceed no really satisfactory explanation is available. ⁵⁷ The difficulty is that although the complexes. Some other type of bonding clearly must also be present in many EDA comtype accounts for some of the bonding ⁵⁰ but is too weak to explain the bonding in all cases. ⁵⁰ stood, but it presumably involves some kind of donor-acceptor interection. plenes. The exact nature of this bonding, called charge-transfer bording, is not well under the acceptor does not have a vacuut orbital. Simple attraction of the dipole induced dipole donor has a pair of electrons to committante (both a donors and a donors are found here). The booding in these cases is more difficult to explain then in the previous case,

Crown Ether Complexes and Cryptates⁶⁰

Figure credere of optimize compleme, see Fosters, Fostense, in Patal The Chemistry of the Quinoscold Composede, pp. 1, Yhlipp New York, 1974, pp. 257-253.

*Spec Blandwinds: Lonzach Kerdal J. Urg. Chem. 1987, St. 1461.

*Figure a credere of subspirioles as acceptions, see Scater, in Patal, Red. 3, pp. 175-222.

*Figure a service of compleme formed by tetrasposed physical and other polyspano samplement, see bladly, in Rappoper, The Chemistry of the Opens Groups, Wiley: New York, 1970, pp. 639-663. See also Factal Aprofession 1987, 199-178. pattern. Examples are 12-covers 4 (19), o deyeloberano-18-covers 6 (11), and 15-covers Crown ethers are large-sing comported containing several oxygen mons, usually in a regular (12). These compounds have the property $^{\alpha}$ of forming complexes with positive ions, gen

Pier retiers, see Bender Chem. Soe. Rev. 1988, 15, 415-501; Kamper, Pellimin Rem. Chem. Rev. 1988, 51

 D4-34C; Bezi Glem. Rev. 1988, 61, 507-68.
 Sec., for consists, Le fevre; Rudford, Siles J. Chem. Soc. B 1988, 1297.
 Speci, for consists, Le fevre; Rudford, Siles J. 3489.
 Specializat; Freezier, J. Am. Ohm. Soc., 1988, 97 3489.
 Specializat; Sec. Advanced; Davina; Mandridot Inclusion. Computers, 5 vol. 97. ed, 3 role.; Academic Press: New York, 1986

"We a brainis, see Annout, Donica, Backlind Relation Companies, 3 villa, Academic Press. New York, 1974.
For authorypiths, see Without of al. Comm. Elater and Annales, 1984.
Chemicry, J. II, and III (1975) Care. Chem. 93, 192, 1937, Springer, Berlin, 1981, 1982, 1982, 1982, 1983; Wegin; Weber Gondele Grouples Complete Complet

*Cook: Caract Byrn: Bowers, Speck; Lists Thinfathon Les. 1974, 4220.
*Discovered by Posteries J. Am. Chen. Bet. 1985; 40:295, 7017. For an account of the discovery, see Schweder;

most cases the loss are held tightly in the center of the cavity. ⁶¹ Each crown other binds

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Str but not Care of The complexes can frequently be prepared as well-defined stamp-and ting K., we while 11 binds K. but not Li. . Similarly, 11 binds Hg. but not Col. or Zm., and different ions, depending on the size of the cavity. For example, 18 binds Live but not

found much use in organic synthesis (see the discussion on p. 363). Chiral cown ethers most frequently used to complex cations, animes, phenots, and often sentral molecules bave have been used for the resolution of racemic mixtures (p. 123); Although cross ethers are Apart from their obvious utility in separating mixtures of cations, a caren ethers have

also been complexed. (see p. 133 for the complexing of saising). **

Magrocycles containing nitrogen or sulfur atoms, "1 e.g., 13 and M. ?! have similar properties, as do those containing more than one kind of heteric atom, e.g., 15,73 16,74 or 17.75 or 18.75 or 17.75 or 18.75 or 1 sometimes called cryptends). The tricyclic cryptend IP has ten binding sites and a spherical cavity. S Another molecule with a spherical cavity (though not a cryptend) is 18, which even more tightly than the monocyclic crown others. Bisyclici and cycles of higher order Biografic molecules like 16 can surround the emplosed son in three dimensions, binding the are called *cryptonia* and the complexes farmed are called cryptater (manacylics are also

⁴⁶For a managraph, was beaute Coled Calest Righting by Falentscycles; Marcel Debter; New York, 1991.

*For reviews of themsodynamic and Month than for the type of interaction, see fant; Brachber; Neskor; Lamb;
Carloscon; Sen Chem. Rev. 1981, 57, 271-394; Denemor; Showley, in Alword; Davier; MacNotel, Red. 60, vol. 3,

Wheth Econory Duke; Dukeymany, Kripismany Acts Chem. Road. 1970, 27, 1783.

"Cortain decimalists of H-corons and D-chem. 2 done vary high reducibility in the companed to the other shall need it ion. See Bostnich; Cared; Pangy Simens, Things Chem. Chem. 2001. Ann. Chem. See. 1988, 1977.

1997; Duke; Egyptand; Fredditzer, Sprind A. Thing. Ene., Chem. Soc. 1971, 199; Duke; Proclabases Fore Appl. 1997; Duke; Egyptand; Fredditzer, Sprind A. Thing. Ene., Chem. Soc. 1971, 199; Duke; Proclabases Fore Appl. Chem. 1988, 1977.

Chem. 1989, 67, 1997.

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1898 or referre of suffus-containing third behaviory for any Vermbers, Eastern Maßer Rep. 1886, 6, 137-254, Eart. Chen. Rep. 1892, 11, 185-671. For a certain of floor containing 5 and N. 500 Raid; Schooler Chen. Sec. Arv. 1894, 19, 239-249.
189 a review of M and In destroying, any Oppolismic, Wingburth Prog. Invoy. Chen. 1881, 13, 123-416.
189 Third States Chen. Company. 1882, 1003.
189 Third States Chen. Ann. Chen. 1883, 15, 1822.
189 Third Lakes Chen. Ann. Chen. 1883, 18, 1802.
189 Third Lakes Chen. Chen. 1883, 18, 1802.
189 Third Lakes Chen. Ann. Chen. 1883, 11, 49-51, Part Appl. Chem. 1877, 49, 57-570.
1893, 3, 339-335, Chericka In Annoual Barles, MacRison, Red. 40, vol. 1, 19, 337-405, Penter Adv. Borry, Raisconne.
1893, 27, 1-26; Lehn Ann. Chen. Res. 1883, 11, 49-51, Part Appl. Chem. 1877, 49, 57-570.

erally metalite ions (though not usually ions of transition metals) or semmonium and sub-

CHAPTER 3

stituted ammonium is no. The crown ether is called the host and the isn is the guest. In

ADDITION COMPOUNDS SI

containing a crown other ring with one or more side chains that can also serve as ligands

An example is 24.

oms and the positive loan.

specific, enabling the boot to pull just one malecule or ion out of a mixture. This is calle

As we have implied, the shillby of these bust mulecules to bind guests is often ver The bonding in these completes is the result of inn-dipole attractions between the heter

"For notions, see Koor, Torottov June.

1; Vigdo I. Am. Olent. Soc. 1977, 99, 4683.

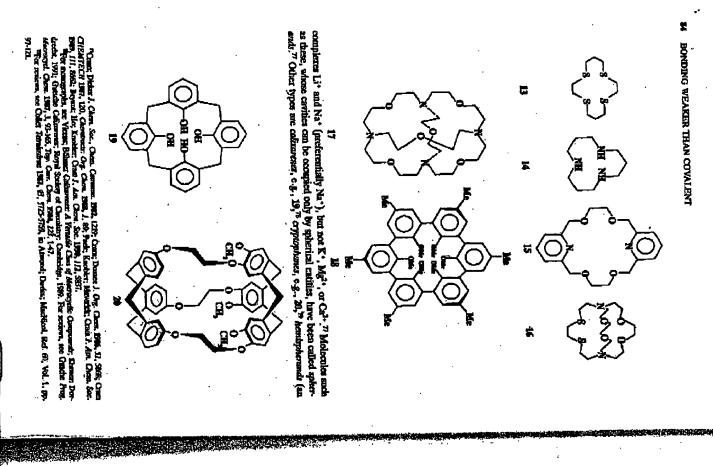
Yoya; Okshara J. A.a. Chem. Soc. 1988, 180, SIL 1974, 13, 814 [Angers, Chem. 13, 1994] Chem. Chemans. 1988, 1853; Gattor

Goldes J. Ann. Charm. So

Chars. Rev. 2598, 59, 265-258; Marger Top.

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Take Case J. Alex. Chem. Soc. 1889, 857, 468



molecule, binds simple cations such as Na+, K+, and Ca++. Luries others are compound arms come out of a central structure. Exemples are 25° and 23.° 23, also called an *octopi* example is 21.27), and podewes. 81 The last-named are host compounds in which two or man

CHAPTER 3

ADDITION COMPOUNDS 1

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BONDING WEAKER THAN COVALENT

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molecular recognition. In general, explands, with their well-defined three-dimensional cavities, are better for this than monocyclic crown eithers or ether derivatives. An example is the heat 25, which selectively block the dictaion 26 (n = 5) rather than 26 (n = 4), and 26 (n = 6) rather than 26 (n = 7). The heat 27, which is water-soluble, forms 1:1 complexes

with neutral aromatic hydrocarbons such as pyrene and fluoranthems, and even (though more wealty) with highestyl and naphthalene, and is able to transport them through an aqueous phase. $^{\rm H}$

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When critisms, use Robelt Anglew, Chees. Int. Ed. Engl. 1998, 73, 245-255 [Anglew, Chees. 162, 261-272], Acc. Chees. Res. 1998, 25, 399-405, Top. Chees. Chees. 1998, 167, 189-210, Med. Struck Energy. 1998, 16, 220-220; Piederlich J. Chiere. Beher. 1998, 67, 813-420; Piederlich J. Chiere. Beher. 1998, 67, 813-420; Piederlich J. Chiere. Edec. 1998, 67, 813-420; Piederlich J. Chiere. Beher. 1998, 67, 813-420; Piederlich J. Chiere. Edec. 1998, 67, 813-820; Piederlich J. Chiere. 1998, 67, 813-8

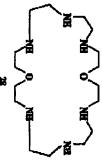
"Magasmana; Magasmana; Solinchied J. Chen, Ser., Chen, Consum, 1979, 772. "Diedarich: Dich J. Am. Chen, Ser., 1986, 1985, 1984; Diedarich: Gibbel J. Ant. Chem. Ser. 1984, 166, 1887 1 des Vogdit; Müber; Wezzer; Louensky Augent. Chem. In. Ed. Engl. 1987, 26, 901 (Angent. Chem. 9s, 595).

CHAPTER 3

ADDITION COMPOUNDS

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Of course, it has long been known that molecular recognition is very important in biochemistry. The action of enzymes and various other biological molecules is entremely specific because these molecules also have host cavities that are able to recognize only one or a few particular (Spec of guest molecules. It is only in recent years that organic chemists have been able to synthesize non-natural bosts that can also perform crude (compared to histogical molecular recognition. The macrocycle 28 has been used as a catalyst, for the hydrolysis of acetyl phosphate and the synthesis of pyrophosphate.



No matter what type of bost, the strongest attractions occur when combination with the great causes the smallest amount of distortion of the host. ¹⁶ That is, a fully prompouzed host will bind better than a host whose molecular shape must change in order to accomodate the guest.

Industria Compensats

This type of addition compound is different from either the EDA complexes or the cover either type of complexes peerfously discussed. Here the host forms a crystal lattice which has spaces large enough for the guest to fit into. There is no banding between the bost and the guest except van der Waals forces. There are two main types, depending on the shape of the space. The spaces in inclusion compoundable in the shape of long tunnels or channels while the other type, often called classrate, or case compounds have spaces that are completely enclosed. In both types the guest melecule must fit into the space and potential guest that are too large or too small will not go into the lattice, so that the addition compount will not form.

One important host molecule suring the inclusion compounds is trea.²⁰ Ordinary crystalline uses is tetragonal, but when a gaset is present, usu crystallizes in a hexagonal lattice containing the gaset in long channels (Figure 3.1).²⁰ The besugonal type of lattice can four only when a gaset molecule is present, showing that van der Waals forces between the bost and the gaset, while small, are executed to the stability of the structure. The district of the channel is about 5 Å, and which molecules can be gaset is dependent only on their

**Hosseld; Lehs J. Am. Ohen. Soi: 1987, 1897, 1947. For a discussion, see Mertor; Marros Act. Chem. Son. 1898, 28, 413-418.

26, 413-418.

26, 60 Chem. Augers. Chem. Inc. 124. Digit. 1888, 25, 1039-1087 [Augers. Chem. 98, 1041-1060].

"For a treatise that include both types, spit Asmoot Daudas, Manfiloul, Rad. 60. For reviews, acc Weber Top Care, Chem, 1987, 160, 1600, Cyclid Tap. Chem. 1987, 140, 71-105; Mari, Wong Tap. Care, Chem. 1987, 140 140-154; For a craims of channels with infilm diapper, are Richary Darno Top. Chem. 1988, 140, 144; Weber: Chengler Tap. Curr. Chem. 1988, 140 "For switchs, use Guideburg Tap. Curr. Class. 1988, 140, 144; Weber: Chengler Tap. Curr. Chem. 1988, 140

"The seriess, see deliberg Roy, Care, Care, 1983, 149, 1444; Richer, Cangler Roy, Core, Close, 1983, 144 45-155; Hest Foot; Helicadetic; Wilson Close, See, Rev. 1978, 7, 49-67. "The a metic of area and discuss helmion compounds, see Talenton; Smooth, in Atmost; Device; MacNikol Ref. 40, vol. 2, pp. 47-47.

pictoire is taken from a paper by Monatel Bhill. Soc. Chin, Fr. 1985, 1013

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